TABLE I
THIOCYANOHYDRINS AND EPISULFIDES

Compd	Recrystn media	Mp, °C	$[\alpha]^{25}D$, deg	Yield, %	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
IIIa	MeOH	158–161	+95	84.2	$C_{22}H_{33}NO_2S$	70.36	8.86	70.67	8.63
IIIb[a]			+10	90.2	$C_{24}H_{35}NO_4S$	66.48	8.14	66.74	8.37
VIIa	EtOH	234–236.5	+113	84.3	$C_{22}H_{33}NO_2S$	70.36	8.86	70.47	8.96
VIIb	MeOH	221–222.5	+28.5	80	$C_{24}H_{35}NO_4S$	66.48	8.14	66.81	8.16
IVa	Me_2CO	168–170	+116	67.5	$C_{21}H_{32}OS$	75.85	9.70	75.95	9.66
IVb	MeOH	189–192	+17	72	$C_{23}H_{34}O_3S$	70.73	8.78	70.32	8.75
VIIIa	Me_2CO–H_2O	165–166	+113.5	68	$C_{21}H_{32}OS$	75.85	9.70	75.98	9.58
VIIIb	Me_2CO–H_2O	167–170	+20	82.6	$C_{23}H_{34}O_3S$	70.73	8.78	70.58	8.91

[a] An oil which resisted crystallization from a variety of solvents.

tion of potassium hydroxide gave the 2,3β-episulfides IV in good yield.

When the 2,3-olefins I were treated with hypobromous acid, the corresponding bromohydrins V were obtained. Treatment of V with sodium carbonate solution afforded the β-epoxides VI. Reaction with thiocyanic acid followed by base as described above gave the 2,3α-episulfides VIII.

The intermediate epoxides II and VI and thiocyanohydrins III and VII as well as the episulfides IV and VIII were evaluated[5] for progestational activity in the McPhail assay[6] and found inactive by injection at a screening dose of 1 mg/day/rat.

Experimental Section[7]

2,3α-Epoxy-5α-pregnan-20-one (IIa).—To a solution of Ia (12.0 g) in benzene (100 ml) was added with stirring and cooling *m*-chloroperbenzoic acid (8.0 g, 85% pure) in benzene (125 ml). The reaction mixture was allowed to stand for 1 hr at 3° and then 0.5 hr at room temperature. The solution was washed repeatedly with 5% $NaHCO_3$ solution followed by H_2O alone, and dried (Na_2SO_4). Solvent removal *in vacuo* and recrystallization from methanol afforded pure IIa (9.6 g, 76%), mp 148–150°, 158–160°, $[\alpha]D$ 110.5°.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.88; H, 10.09.

2,3α-Epoxy-5α-pregnan-17α-ol-20-one acetate (IIb) was prepared from Ib as described above, mp 212–214°, $[\alpha]D$ +12°, in 87.6% yield.

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 74.00; H, 9.06.

3α-Bromo-5α-pregnan-2β-ol-20-one (Va).—To a solution of Ia[3,4] (20.0 g) in cold H_2O was added with stirring a mixture of N-bromosuccinimide (13 g), $HClO_4$ (11.3 g, 60%), and H_2O (125 ml) over 15 min. The reaction was stirred for 2.5 hr and poured into ice and H_2O. The precipitate was collected, washed with H_2O, dissolved in chloroform, and dried (Na_2SO_4 containing Darco). Removal of the solvent *in vacuo* left a solid which was recrystallized from methanol to give Va (15.45 g, 56.4%), mp 206–208°. Further recrystallization from ethanol gave pure Va (12.3 g), mp 210.5–212°, $[\alpha]D$ +126°.

Anal. Calcd for $C_{21}H_{33}BrO_2$: C, 63.49; H, 8.37. Found: C, 63.47; H, 8.31.

3α-Bromo-17α-hydroxy-5α-pregnan-2β-ol-20-one (Vb) was prepared from Ib[3] as described above, mp 220–223.5°, $[\alpha]D$ +126° in 76.5% yield.

Anal. Calcd for $C_{23}H_{35}BrO_4$: C, 60.65; H, 7.75. Found: C, 60.43; H, 7.62.

2,3β-Epoxy-5α-pregnan-20-one (VIa).—To a solution of Va in tetrahydrofuran (250 ml) was added Na_2CO_3 (1.5 g) in H_2O (175 ml). The reaction mixture was allowed to stand at room temperature for 2.5 days. Dilution with H_2O gave a precipitate which was collected, washed with H_2O, and air dried. Recrystallization from methanol gave pure VIa (4.1 g, 80%), mp 174–175.5°, $[\alpha]D$ +119°.

Anal. Calcd for $C_{21}H_{32}O$: C, 79.70; H, 10.19. Found: C, 79.92; H, 10.16.

2,3β-Epoxy-5α-pregnan-17α-ol-20-one acetate (VIb) was prepared from Vb as described above, mp 184–185°, $[\alpha]D$ +29°, in 82% yield.

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.85; H, 9.10.

2β-Thiocyano-5α-pregnan-3α-ol-20-one (IIIa). General Method.—To a mixture of potassium thiocyanate (88 g) in H_2O (43 ml) and ether (300 ml) containing a few ice chips was added H_3PO_4 (132.8 g) in small portions with continuous agitation. The solution washed with two 25-ml portions of cold H_2O and dried briefly (Na_2SO_4). To a solution of IIa (8.0 g) in ether (60 ml) was added the freshly prepared ethereal thiocyanic acid. The reaction was allowed to stand for 2 days at room temperature. The solution was washed with 5% Na_2CO_3 until neutral. After washing with H_2O and drying (Na_2SO_4 containing Darco), solvent removal left a white solid. Recrystallization from methanol gave pure IIIa (6.2 g, 84.2%), mp 158–161°.

2,3β-Epithio-5α-pregnan-20-one (IVa). General Method.—To a warm solution of IIIa (1.0 g) in methanol (25 ml) was added KOH (0.5 g) in methanol (5 ml) with stirring. The reaction was allowed to stand at room temperature for 2 hr. A needlelike precipitate gradually formed as the reaction progressed. Water was added to the mixture and the product was collected, washed with H_2O, and air dried. Recrystallization from acetone gave pure IVa (0.6 g, 67.5%), mp 168–170°.

(5) The author thanks Drs. R. L. Elton and E. F. Nutting for furnishing this biological information.

(6) M. K. McPhail, *J. Physiol.* (London), **83**, 145 (1934).

(7) The elemental analysis and optical rotations in chloroform at ambient temperatures were furnished by Mr. E. Zielinski and Mr. J. Damascus of our analytical department under the supervision of Dr. R. T. Dillon. The melting points were obtained on a Fisher-Johns apparatus and are corrected.

Totally Synthetic Steroid Hormones. X.[1] Some (±)-13β-Ethyl-7α-methylgonane Derivatives

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The interesting steroid hormonal activity reported for a number of 7α-methyltestosterone[2] and 7α-methyl-19-nortestosterone[3] derivatives has induced us to extend our studies on the structure–biological activity relationships of 13β-ethyl- and higher alkylgonane derivatives[4] to various (±)-13β-ethyl-7α-methylgon-4-en-3-ones. Here we report the synthesis of the ketones II (R = H; R^1 = H, C_2H_5, and C≡CH; R^2 = CH_3) and compare their anabolic, androgenic, and progesta-

(1) Part IX: G. Greenspan, L. L. Smith, R. Rees, T. Foell, and H. E. Alburn, *J. Org. Chem.*, **31**, 2512 (1966).

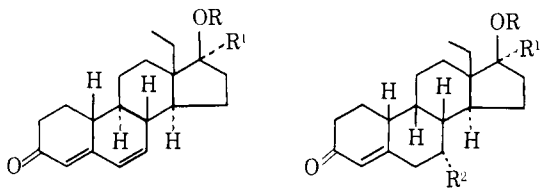
(2) J. A. Campbell and J. C. Babcock, *J. Am. Chem. Soc.*, **81**, 4069 (1959).

(3) J. A. Campbell, S. C. Lyster, G. W. Duncan, and J. C. Babcock, *Steroids*, **1**, 317 (1963).

(4) (a) H. Smith, *et al.*, *Experientia*, **19**, 394 (1963); *J. Chem. Soc.*, 1172 (1964), and references therein cited.

tional activities with the same activities of the corresponding 7-demethyl homologs.

The ketones II (R = H; R^1 = H and C_2H_5; R^2 = CH_3) were made through the cuprous chloride catalyzed addition of methylmagnesium bromide to the respective gonadienones I (R = $COCH_3$; R^1 = H and C_2H_5) (*cf.* ref 2 and 3), which were obtained from the corresponding gon-4-en-3-ones by Zderic and co-workers' general method.[5] The α configuration is assigned to the 7-methyl group by analogy with the formation of 17β-acetoxy-7α-methylestr-4-en-3-one from 17β-acetoxyestra-4,6-dien-3-one by the same procedure.[3] The ketone II, (R = R^1 = H; R^2 = CH_3) was obtained directly from the Grignard addition reaction with I (R = $COCH_3$; R^1 = H), presumably because of ester hydrolysis under the acid work-up. A similar treatment of I (R = $COCH_3$; R^1 = C_2H_5), however, gave the acetate II (R = $COCH_3$; R^1 = C_2H_5; R^2 = CH_3), from which the corresponding 17β-ol was obtained by reduction with lithium aluminum hydride in ether, followed by manganese dioxide oxidation in chloroform. Application of an analogous sequence to the preparation of the ketone II (R = H; R^1 = C≡CH; R^2 = CH_3) was less efficient, and this compound was best obtained from the ketone II (R = R^1 = H; R^2 = CH_3) by conversion to the 3-ethylene ketal, oxidation of the 17-hydroxyl to a 17-carbonyl group, interaction with lithium acetylide, and acid hydrolysis of the resulting ethynyl alcohol.



I II

Biological Activities.—Androgenic and anabolic activities were estimated by the Hershberger test,[6] and progestational activities by the Clauberg test.[7]

TABLE I

BIOLOGICAL ACTIVITIES OF (±)-13β-ETHYL-17β-HYDROXYGON-4-EN-3-ONES (II, R = H)

R^1	R^2	Anab[a]	And[b]	Prog[c]
H	CH_3	300	60	7
C_2H_5	CH_3	48	70	50
C≡CH	CH_3	27	26	20
H	H	54	27	3
C_2H_5	H	350	17	300
C≡CH	H	70	8	915

[a] Anabolic potency expressed in terms of testosterone propionate (= 100). [b] Androgenic potency expressed in terms of testosterone propionate (= 100). [c] Progestational potency expressed in terms of progesterone (= 100).

Experimental Section[8]

(±)-17β-Acetoxy-13β-ethylgona-4,6-dien-3-one (I, R = $COCH_3$; R^1 = H).—(±)-13β-Ethyl-17β-hydroxygon-4-en-3-one[4] (3 g) was refluxed in acetic anhydride–acetyl chloride–pyridine (45:24:2.4 ml) for 3 hr. The solvents were evaporated under reduced pressure and the residue was partitioned between water and benzene–ether. The organic solution was washed, dried, and evaporated, and the residue was triturated with hot ether to give crude (±)-3,17β-diacetoxy-13β-ethylgona-3,5-diene (3.125 g), mp 148–156°, λ_{max} 238 mμ (ϵ 19,500). N-Bromosuccinimide (0.5 g) was added to the foregoing diacetate (1 g) in acetone–water–acetic acid (106:27.2:2.72 ml) containing pyridine (0.6 ml) and sodium acetate (2.72 g) at 0°, and the mixture was stirred for 3 hr at −5 to +5°, added to ice-cold brine (800 ml), and extracted with ether. The ether solution was washed, dried, and concentrated below 15°. Calcium carbonate (3 g) and dimethylformamide (70 ml) were added, the remaining ether was distilled, and the suspension refluxed for 1 hr. The mixture was filtered, the residue was washed with ether, the filtrate and washings were combined and added to brine, and the mixture was extracted with ether. Recrystallization of the product from ethyl acetate–hexane gave the dienone (0.475 g), mp 163–166°, λ_{max} 283 mμ (ϵ 24,370).

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.8; H, 8.6. Found: C, 76.5; H, 8.6.

(±)-13β-Ethyl-17β-hydroxy-7α-methylgon-4-en-3-one (II, R = R^1 = H; R^2 = CH_3).—The foregoing gonadienone (2 g) in tetrahydrofuran (THF) (20 ml) was added to ethereal methylmagnesium bromide (3 *M*)–THF (16:20 ml) containing cuprous chloride (0.3 g) at 0°. The mixture was stirred for 20 min and poured into ice-cold brine containing HCl. The product was collected with ether, chromatographed on neutral alumina, and recrystallized from ethyl acetate–hexane to give the gonenone (0.56 g), mp 152–154°, λ_{max} 242 mμ (ϵ 16,730).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.4; H, 10.0. Found: C, 79.1; H, 9.9.

3,17β-Diacetoxy-13β,17α-diethylgona-3,5-diene.—13β,17α-Diethyl-17β-hydroxygon-4-en-3-one[4] (3 g) was refluxed for 2 hr in acetic anhydride–acetyl chloride–pyridine (48:24:2.4 ml). The solvents were removed under reduced pressure and the residue was partitioned between benzene–ether and water. The product from the organic layer was triturated with ether and washed with hexane to give the diacetate (3.5 g), mp 122–125°, λ_{max} 238 mμ (ϵ 18,200).

Anal. Calcd for $C_{25}H_{36}O_4$: C, 75.0; H, 9.1. Found: C, 74.6; H, 9.1.

(±)-17β-Acetoxy-13β,17α-diethylgona-4,6-dien-3-one (I, R = $COCH_3$; R^1 = C_2H_5).—N-Bromosuccinimide (3.4 g) was added with stirring to the foregoing diacetate (3.4 g) in acetone–water (130:16 ml) containing sodium acetate (2.4 g) at 0°. The mixture was stirred at 0° for 3 hr, poured into ice-cold brine, and extracted with ether. The ether solution was concentrated below 20°. Calcium carbonate (10 g) and dimethylformamide (235 ml) were added, the ether was distilled, and the remaining suspension refluxed for 1 hr. The product was chromatographed on neutral alumina and recrystallized from ether to give the gonadienone (1.6 g), mp 151–153°, λ_{max} 282 mμ (ϵ 28,700).

Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.5; H, 9.05. Found: C, 77.1; H, 9.05.

(±)-17β-Acetoxy-13β,17α-diethyl-7α-methylgon-4-en-3-one (II, R = $COCH_3$; R^1 = C_2H_5; R^2 = CH_3).—The foregoing dienone (1 g) in THF (10 ml) was added under nitrogen with stirring to ethereal methylmagnesium bromide (3 *M*)–THF (8:10 ml) containing cuprous chloride (0.2 g) at 0°. The mixture was stirred for 1 hr, poured into brine containing HCl, and extracted with ether. The product was chromatographed on neutral alumina and recrystallized from ether–hexane to give the gonenone (0.25 g), mp 142–144°, λ_{max} 242 mμ (ϵ 18,250).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.4; H, 9.7. Found: C, 77.4; H, 9.7.

(±)-13β,17α-Diethyl-17β-hydroxy-7α-methylgon-4-en-3-one (II, R = H; R^1 = C_2H_5; R^2 = CH_3).—The foregoing acetate (0.49 g) was refluxed with $LiAlH_4$ (0.4 g) in ether (60 ml) for 1.5 hr. Saturated aqueous tartaric acid (40 ml) was added to the cooled solution. The product in chloroform (50 ml) was stirred at room temperature with MnO_2 (2.5 g) for 3 hr. Recrystallization of the product from ether gave the ketol (0.11 g), mp 130–132°, λ_{max} 244 mμ (ϵ 16,500).

Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.4. Found: C, 79.8; H, 10.2.

(±)-13β-Ethyl-17α-ethynyl-17β-hydroxy-7α-methylgon-4-en-3-one (II, R = H; R^1 = C≡CH; R^2 = CH_3).—The gonenone II (R = R^1 = H; R^2 = CH_3) (1.35 g) was refluxed for 6 hr in

(5) J. A. Zderic, A. Bowers, H. Carpio, and C. Dierassi, *J. Am. Chem. Soc.*, **80**, 2596 (1958).

(6) L. G. Hershberger, E. G. Shipley, and R. K. Meyer, *Proc. Soc. Exptl. Biol. Med.*, **83**, 175 (1953).

(7) R. L. Elton and R. A. Edgren, *Endocrinology*, **63**, 464 (1958).

(8) Melting points were determined in capillary tubes (Thomas–Hoover apparatus) and are uncorrected. Ultraviolet absorption spectra were recorded in 95% ethanol.

benzene (100 ml) containing ethylene glycol (10 ml) and toluene-*p*-sulfonic acid (from the hydrate, 0.067 g) (Dean–Stark apparatus). The product was refluxed for 3.5 hr with aluminum isopropoxide (0.8 g) in toluene–cyclohexanone (50:10 ml), and the resulting crude ketone was stirred for 2 hr in a stream of acetylene with dimethylacetamide (50 ml) containing lithium acetylide–ethylenediamine complex.[9] The mixture was added to crushed ice and extracted with ether. The product was stirred for 1.5 hr under nitrogen in methanol–3 *N* HCl–water (50:3:2 ml) and the solution was poured into brine and extracted with ether. Chromatography of the product on Florex and recrystallization from ethyl acetate–hexane gave the gonenone (0.55 g), mp 182–184°, λ_{max} 240 mμ (ε 16,500).

Anal. Calcd for $C_{22}H_{36}O_2$: C, 80.9; H, 9.3. Found: C, 80.6; H, 9.1.

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(9) O. F. Beumel, Jr., and R. F. Harris, *J. Org. Chem.*, **28**, 2775 (1963).

3-Phenylcinnolines. III.[1] Derivatives of Hydroxy-3-phenylcinnolines

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A few cinnoline derivatives were prepared for pharmacological testing by alkylation of 4- and 4′-hydroxy-3-phenylcinnolines. These are listed in Table I, along with methyl derivatives for comparison of spectral data.

Alkylation of 3-phenyl-4-cinnolinol (**15**) with methyl iodide gave a mixture of the 1 and 2 isomers (**10** and **11**) in about a 5:3 ratio, while diazomethane furnished only the 1 derivative.[2] That these isomers are quite distinct from the 4-methoxy isomer (**12**) is shown by the spectral data and by the large depression of their mixture melting points. Compound **10** was assigned as the 1 isomer on the following evidence: (a) the slightly higher field absorption of its methyl protons in the nmr compared to those of the other isomer has been observed with other similar pairs of cinnoline isomers;[3] (b) the infrared, ultraviolet, and nmr spectra of **10** show great similarity (Table I) to those of the starting material, **15**, which has been assigned structure I,[1b] in common with other 4-hydroxycinnolines;[3] (c) one would expect the less sterically hindered product to predominate,[3] particularly with larger alkyl halides (see below); (d) the isolation of only one isomer using diazomethane which should not isomerize **15** from structure I tends to confirm the assignment; (e) finally, the pattern of aromatic protons in the nmr is interesting. The two 2′-protons on the 3-phenyl ring (which is probably coplanar) are deshielded and appear in several of these compounds at about 475–495 cps.[4] With the 8-proton (about 500–520 cps), there are then three protons from 475 to 520 cps (and the remainder between 400 and 475 cps) for compounds of structure I in Table I. However, **11**, the 2 isomer, has only one proton in the 475–520-cps region. This may be explained by steric interference of the 2-methyl, causing the phenyl ring to twist out of coplanarity and eliminating the deshielding of the 2′-protons. The same effect is also observed with the 1- and 2-oxides of 3-phenylcinnoline,[1b] the latter showing only the 4-proton below 480 cps (the 8-proton is shielded in the 2 isomer[1b]).

The products[2,5] using other alkyl halides were also assigned as 1 isomers having very similar spectra to those of **10**. Lacking the other isomer in these cases, the position of the α-CH_2 protons cannot be used for evidence because of the small difference in the two isomers (5 cps for **10** and **11**), but three aromatic protons in the 475–520-cps region were observed for these derivatives.

Reactions of 4-chloro-3-phenylcinnoline with the sodium salt of the corresponding alcohol furnished the 4-alkyloxy derivatives, **2** and **12**, the former being readily hydrolyzed in acid. On distillation these rearranged to the 1-alkyl-4-cinnolones,[2] **1** and **10**. To our knowledge this type of rearrangement has not been noted before in the cinnoline series, but it is well known for 4-alkoxyquinolines.[5]

Alkylation of **14** gave the corresponding alkoxy derivatives, **3**, **7**, and **9**, whose structures were substantiated by the similarity of their spectra with those of **13** and **14**.

Compound **7** showed about 2% the activity of hydrochlorothiazide as a diuretic in rats. Compounds **4** and **5** had only borderline activity against yeast-induced foot edema in the rat. The most interesting of the series, **3**, was about four times as active orally as phenylbutazone in this latter test, but toxic side reactions in the cotton pellet granuloma test discouraged further study.[6]

Experimental Section[7]

1-(2-Diethylaminoethyl)-3-phenyl-4-cinnolone (Table I, 1). A. By Alkylation of 15.—A solution of 6.6 g of 3-phenyl-4-cinnolinol,[1b] 3.3 g of KOH, and 7.0 g of 2-diethylaminoethyl

(1) (a) Paper I: H. S. Lowrie, *J. Med. Chem.*, **9**, 664 (1966); (b) paper II: H. S. Lowrie, *ibid.*, **9**, 670 (1966).

(2) Spectral data on the crude reaction product indicated predominantly the 1 isomer (I), but the presence of a small amount of the 2-isomer (II) cannot be ruled out. Only in preparation of **10** and **11** with methyl iodide was the 2 isomer actually isolated.

(3) D. E. Ames, R. F. Chapman, and D. White, *J. Chem. Soc.*, 470 (1966), and references therein.

(4) When **1** was prepared by alkylation of **15** it was assumed that the low-field absorption (273 cps) of the α-CH_2 (see Table I) indicated attachment to oxygen rather than nitrogen. In addition, the position of the 8-hydrogen at 500–510 cps seemed to support III rather than I since the 8-H atoms in various 3-phenyldihydrocinnolines[1b] are moved appreciably upfield. Recent papers on the structure and alkylation of cinnolines, summarized in ref 3, forced the reexamination reported here, and the preparation of **2**, Table I, and the methyl derivatives, **10–12**, for comparison. The structures assigned by the author in U. S. Patent 3,239,524 (1966) should be I, not III.

(5) R. C. Elderfield, "Heterocyclic Compounds," Vol. 4, John Wiley and Sons, Inc., New York, 1952, pp 152–153.

(6) These tests are described in ref 1. The relative potencies given refer to the ratio of the weights of equally effective doses. We are indebted to Drs. F. J. Saunders, E. F. Nutting, and D. L. Cook, and Mr. R. S. Jacobs and their staffs for these screening data.

(7) All melting points are corrected and were taken in a Hershberg apparatus. Microanalyses were performed by the Microanalytical Department under Dr. R. T. Dillon. Infrared spectra were taken in chloroform solution on a Beckman IR-4, and the ultraviolet spectra were taken in methanol on a Beckman DK-2. Nmr, recorded on a Varian A-60, is given in cycles per second (cps) of downfield shift from tetramethylsilane as an internal reference standard in $CDCl_3$.